Lecture:

CNS Infection

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Meningitis

- Meningitis is an inflammatory disease of the meninges, the tissues surrounding the brain and spinal cord, and is defined by an abnormal number of white blood cells in the CSF.
- Meningitis is an emergency.
- Mortality is often high.

* meningism => irritation of meninges without inflammation
  ↳ Normal WBC هنا

Classification (Causes) of Meningitis

neutrophil : dominant ال , عدد WBC بالآلاف

I. Septic Meningitis: pyogenic bacterial. → strep., staph.

II. Aseptic Meningitis: aseptic meningitis is an illness characterized by serous inflammation of the meninges, usually with **mononuclear pleocytosis.**

بتكون WBC من عشرات لميات وال dominant بتكون ال lymphocytes

1. **Viral:** Enteroviruses, Coxsackie, Poliomyelitis, Mumps, Herpes simplex, HIV, Epstein-Barr virus, Varicella-zoster virus.
2. **Bacterial:** mycoplasma pneumonia, mycobacterium tuberculosis.
3. **Fungal:**

4. **Parasites:** toxoplasmosis.

5. **Spirochateal infections:** syphilis, leptospirosis.

6. **Drugs :**

   Nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics (eg, trimethoprim-sulfamethoxazole, ciprofloxacin, cephalexin, metronidazole), azathioprine, IVIG, vaccines, allopurinol. → T. of gout

7. **Systemic diseases:**

   Sarcoidosis, malignancy, posttransplantation, SLE, CNS vasculitis, Behçet disease.

* Causes of recurrent septic meningitis ||
  otitis media , Sinusitis , fistula B/w sinuses in subarachnoid space.

Epidemiology of Bacterial "Septic" Meningitis

- Incidence is between 3-5 per 100,000.
- Approximately 1.2 million cases of bacterial meningitis occur annually worldwide.
- Meningitis is among the 10 most common infectious causes of death.

Septic Meningitis

- **Bacterial meningitis can be:**
  1. **Community-acquired "Streptococcus pneumoniae, Neisseria meningitidis".**
  2. **Healthcare-associated "Staphylococci and aerobic gram-negative bacilli".**
- **Healthcare-associated** bacterial meningitis occur in patients after neurosurgical operation and in patients with internal or external ventricular drains, or following trauma with leak of CSF.

Vp shunt · اي عاملين

open fracture · اي عندهم

leak CSF ← open Trau ← Skull fracture

Causative Organisms

In Neonates (< 30 days):
Gm (-) bacilli (e.g. E. Coli, Klebsiella), Haemophilus influenzae.

In Children (1 month to 15 years):
Haemophilus influenzae, Pneumococcus, Meningococcus (Neisseria meningitidis).

In Adult:
Pneumococcus, Meningococcus.

Elderly: S. aureus, Haemophilus influenzae, E. coli, Pseudomonas, Listeria monocytogenes (a gram-positive bacillus).

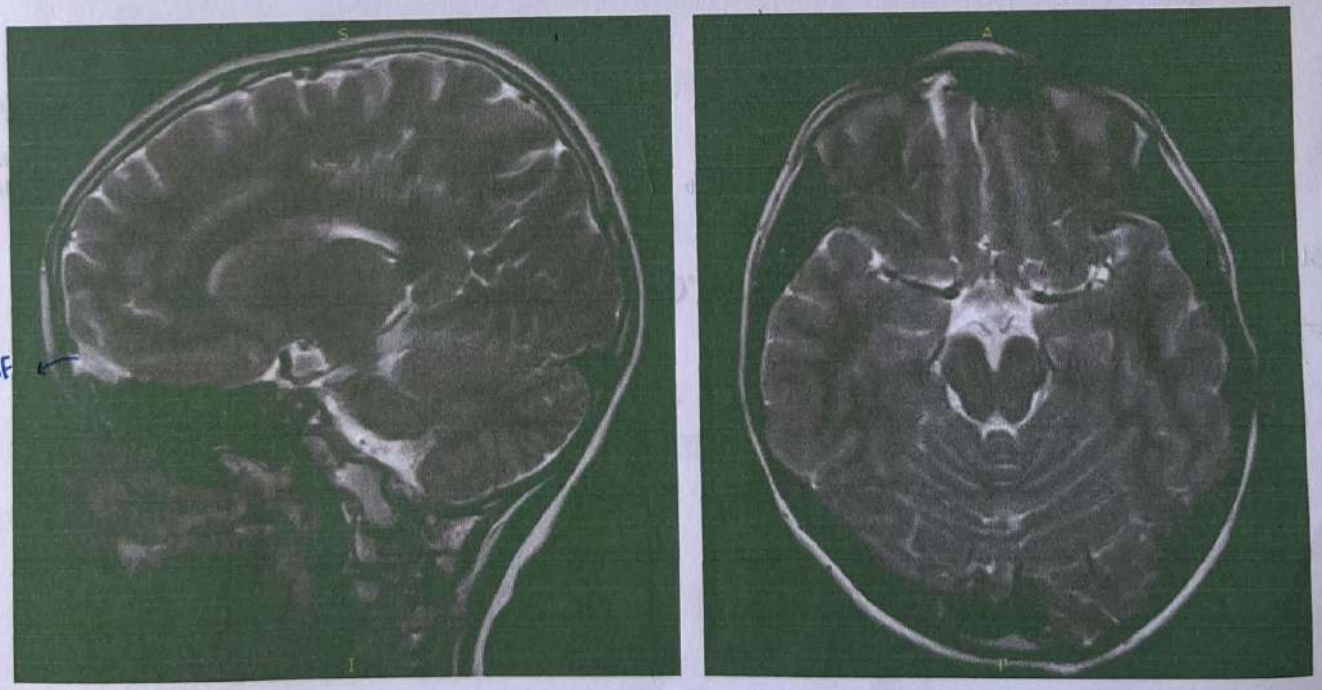
لـ لذلك اي عمر > 50 y وعنده meningitis

هنضيف لعلاج : ampicillin .. 2g كل 4-6 ساعات

Bacterial Meningitis

Microorganisms reach the meninges either by:

- Direct extension from the ears, nasopharynx, paranasal sinuses.
- Head injury with leak of the CSF.
- Congenital meningeal defect (meningomyelocele).
- Bloodstream spread.
- Immunocompromised patients (e.g. HIV, cytotoxic drug therapy).
- CSF shunt.



Right Frontal Sinus Fistula

Persons at Risk

- Pregnant women.
- Infants and children younger than 5 years of age.
- Adults older than 60 years of age.
- Immunocompromisde pt.
- Close contact to the pt.
- Chronic liver and renal disease. , chronic dialysis
- Splenic dysfunction and splenectomy.
- DM.
- Skull fracture and leak of CSF.
- VP shunt.
- Otitis media.
- People with alcoholism.
- People with cancer, especially those receiving chemotherapy and radiotherapy.
- People who have received transplantation.

Diagnosis

History:

- Complaint. → headach, Neck Pain, lever, repeated vomitus, photo- or phono-phopia
- History of present illness. الاعراض بتكون الها ساعات - ايام مش sudden onset زي subarach hemorrhage
- Past medical and surgical history.
- Contact.
- Vaccination.

Clinical Manifestations and Symptoms

The classical clinical triad is:

- Fever,
- Headache,
- Neck stiffness.



Photophobia

Clinical Manifestations and Symptoms

1. **Prodromal Features:**
   Respiratory infection, otitis media.
2. **Meningeal Symptoms:**
   Severe headache, positive meningeal irritation signs "neck stiffness" and photophobia.
3. **Systemic Signs:**
   High fever and skin rash "petechial" in meningococcal meningitis.

   خاصة بال TB menigitis ، لانه بصيب base of skull
4. **Associated neurological signs:**
   Impaired conscious level, seizure, cranial nerve palsies, sensoroneural deafness "20%", focal neurological symptoms and papilloedema "10%".

خاصة بـ gram + diplococci : strepto.

Pathogenesis of Meningococcemia

- Diffuse vasculitis and disseminated intravascular coagulation (DIC).
- Leukocyte-rich fibrin in small blood vessels.
- Focal hemorrhage and necrosis.
- Purpura in skin and organs due to focal hemorrhage.
- **Fatal diseases due to:**
  - **DIC**
  - **Myocarditis**
  - **Waterhouse-Friderichsen Syndrome:**

severe hypotension ← بصير diffuse adrenal gland hemorrhage.

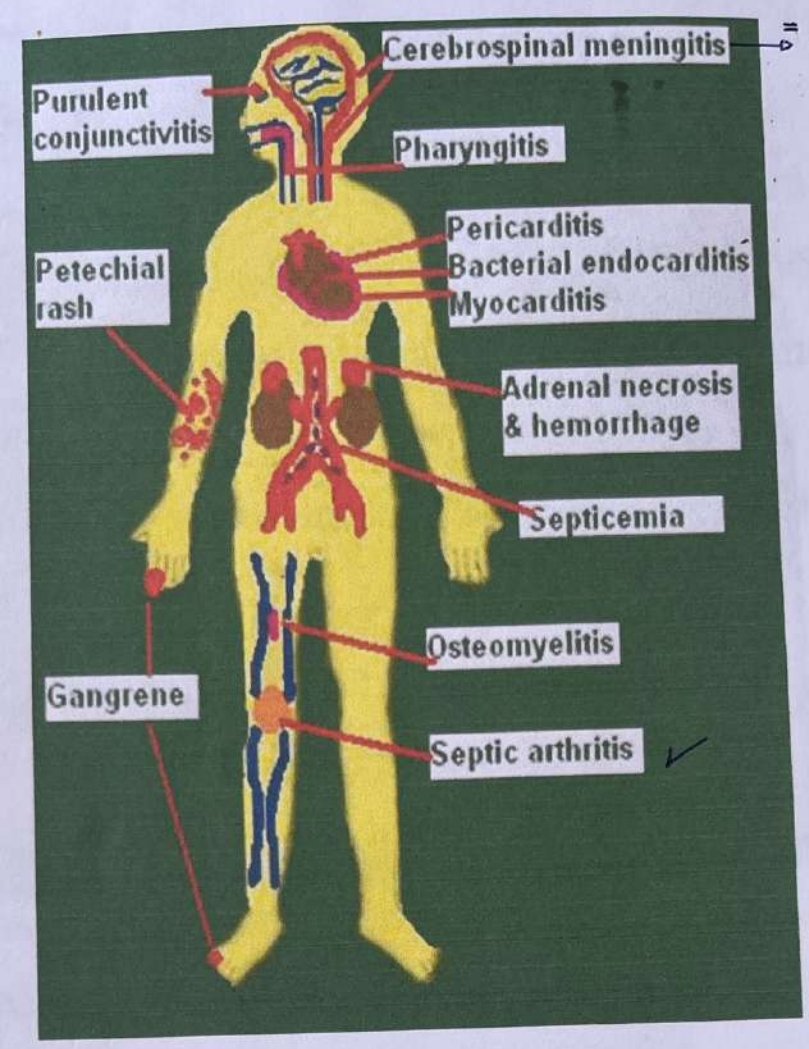
* Petechial rash ...> بالـ B.V small فيحصل leukocyte rich Fibrin لانه عندهم

local hemorrhage + necrosis

Clinical Manifestations of Meningococcal Infection

- Bacteremia without sepsis.
- Meningococcemia without meningitis.
- Meningitis with / without meningococcemia.
- Meningoencephalitis.

* مين الأخطر ؟ ~~meningitis~~ meningococcemia without meningitis



= meningococcal meningitis





Poor Prognotic Factors of Meningococcal Infection

- ✓ Hypothermia.
- ✓ Extreme hyperpyrexia.
- ✓ Recurrent seizures.
- ✓ Extremes of age.
- ✓ Short period between onset and admission.
- ✓ The absence of meningitis in patients with meningococcemia. → Short aggressive bacteria
- ✓ Wide spread skin lesion (purpura fulminans).
- ✓ DIC.
- – Shock.
- ✓ Leukopenia/thrombocytopenia /acidosis.

TB Meningitis

- Bacterial aseptic meningitis by mycobacterium.
- Meningitis is commonest manifestation of CNS TB.
- It usually result from bacteraemia following the initial phase of primary pulmonary TB.
- **The clinical features of TB meningitis result from:**
  - **Infection.**
  - **Exudation:** which may obstruct the basal cisterns and result in hydrocephalus.
  - **Vasculitis:** secondary to inflammation around vessels, resulting in infarction of brain and spinal cord.

Clinical Features of TB Meningitis

- Non-specific prodromal symptoms develop over 2-8 weeks.
- **Stage-1 (Early):** Non-specific symptoms, fever, lethargy.
- **Stage-2 (Intermediate):** confusion, cranial nerve paresis, meningeal irritation signs, seizures, vasculitis (hemiparesis, Quadriparesis, ataxia, dysarthria).
- **Stage-3 (Advanced):** Coma.

Investigation of TB Meningitis

- CBC, blood chemistry: anemia, leucocytosis, hyponatremia. , liver, renal function test → T. عشان ال
- **CSF:** cells 50-4000/mm3, predominantly lymphocytes with low glucose < 50% blood glucose, protein > 1g/dl, acid-fast stain, culture for M. tuberculosis (50-80% positive), Polymerase chain reaction (PCR).
- Chest X-ray. → Pulm. TB عشان اذا في
- Brain CT, MRI.

to detect infarction

The Neurologic Complications of Bacterial Meningitis

- ❖Impaired mental status and intellectual impairment.
- ❖Increased intracranial pressure and cerebral edema.
- ❖Seizures.
- ❖Focal neurologic deficits (eg, cranial nerve palsy, hemiparesis).
- ❖Cerebrovascular abnormalities.
- ❖Sensorineural hearing loss.
- ❖Brain abscess.
- ❖Obstructive hydrocephalus.

Investigation

- **CBC, blood chemistry:** check serum electrolytes, renal function.
- **Coagulation studies.**
- **Blood cultures.**
- **Skin smear:** in meningococcal infection.
- **Fundus examination.**
- **Brain CT:** in some cases.
- **CSF examination.**
- **PCR:** Polymerase Chain Reaction.
- **Chest X-ray** (pneumonia), **skull X-ray** (fracture) & **sinus X-ray** (sinusitis).

Gram Stain



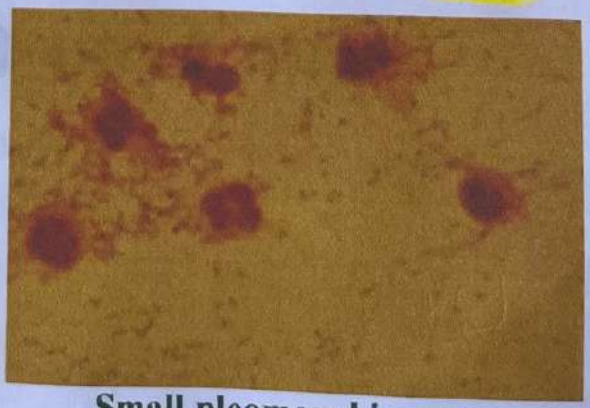
Gram-negative diplococci suggest meningococcal infection



Gram-positive diplococci suggest pneumococcal infection



Gram-positive rods and coccobacilli suggest listerial infection



Small pleomorphic gram-negative coccobacilli suggest Haemophilus influenzae infection

Diagnosis

Lumbar Puncture

Patient with suspected meningitis presented to your clinic

When you should make brain CT scan prior to lumbar puncture ???



Obtain CT scan before lumbar puncture in:

- Patients who are older than 60 years.
- Patients who are immunocompromised.
- Patients with known CNS lesions.
- Patients who have had a seizure within 1 week of presentation.
- Patients with abnormal level of consciousness.
- Patients with focal findings on neurological examination.
- Patients with papilledema (optic N swelling) seen on physical examination with clinical suspicion of elevated ICP.
- Patients with suspected subarachnoid hemorrhage (SAH).

Prognosis of Bacterial Meningitis

- The mortality rate increases with increasing age.
- In a US population-based surveillance study between 2003 and 2007, the case-fatality rate of bacterial meningitis in adults was **16.4%:**
  - **8.9%** among patients between 18 and 34 years of age.
  - **22.7%** among patients ≥65 years of age.

Management of Meningitis

- Administer adequate analgesia.
- Correction of fever.
- Fluid management.
- Dexamethasone in bacterial meningitis.
- **If meningoencephalitis is suspected:** intravenous acyclovir until HSV infection can be excluded.
- **If bacterial meningitis cannot be excluded:**
  Use **ceftriaxone + vancomycin or ceftriaxone + penicillin** until a pyogenic bacterial cause is ruled out.
- Symptomatic therapy.
- Treatment of complications.

Empiric Therapy of Bacterial Meningitis

I. In patients, without immunodeficiency with normal renal function, should be treated empirically with the following regimen until culture and susceptibility data are available:

Ceftriaxone - 2 g IV every 12 hours
OR
Cefotaxime - 2 g IV every 4-6 hours

PLUS
Vancomycin - 30 to 60 mg/kg IV per day in two or three divided doses

PLUS
In adults ≥50 years of age (Listeria monocytogenes):
Ampicillin — 2 g IV every 4 hours

II. An appropriate regimen in patients with impaired cell-mediated immunity and with normal renal function is:

Vancomycin - 30 to 60 mg/kg IV per day in two or three divided doses

PLUS
Ampicillin - 2 g IV every 4 hours

PLUS EITHER
Cefepime - 2 g IV every 8 hours

OR
Meropenem - 2 g IV 8 eight hours

III. Empiric therapy in **nasocomial infection** (ie, following head trauma or after neurosurgery): gram-negative bacilli, and streptococci, staphylococcus aureus must cover both gram-positive and gram-negative. Appropriate regimens in patients with normal renal function, pending culture results and susceptibility testing, are:

Vancomycin - 30 to 60 mg/kg IV per day in two or three divided doses

PLUS
Cefepime - 2 g IV every 8 hours

OR
Meropenem — 2 g IV 8 eight hours

IV. In patients, with suspected meningococcal meningitis (petechial skin rash), should be treated empirically with the following regimen until culture and susceptibility data are available:

Ceftriaxone - 2 g IV every 12 hours
OR
Cefotaxime - 2 g IV every 4-6 hours

PLUS
Penicillin G - 4 million units IV every four hours
The usual dose in pediatrics is 300,000-40,000 units/kg per day

Steroids Therapy in Meningitis

- Corticosteroids are avoided in aseptic meningitis because of their inhibitory effects on host immune responses.
- Glucocorticoids, such as dexamethasone, are useful when meningitis is associated with signs of increased intracranial pressure and for prevention of sensoroneural deafness .

Duration of Treatment

- Dependent on infecting organism
  - **Average of 10-14 days**

- **Meningococcus (Neisseria meningitidis)** - 7 days
- **Haemophilus influenzae** - 7 days
- **Pneumococcus (Strep. Pneumonia)** - 10-14 days
- **Aerobic gram-negative bacilli (bacilli (e.g. E. Coli, Klebsiella)** - 21 days

Antiviral Therapy

❖ Effective antiviral therapy (Acyclovir) is available against HSV-1, varicella, and cytomegalovirus.

❖ In immunosuppressed patients, long-term therapy may be necessary.

Prevention

- Hand washing and other general good health measures.
- Effective vaccines are available for polio, measles, mumps, and rubella.

Viral encephalitis

- Viral encephalitis can be either **primary** or **postinfectious.**
- **Primary encephalitis:** is characterized by primary viral invasion of the CNS.
- **Postinfectious encephalitis:** is an immune-mediated disease (also called acute disseminated encephalomyelitis or ADEM), a virus cannot be detected. Perivascular inflammation and demyelination are prominent in this entity.

Viral Pathogens in Primary Encephalitis

- **A common cause:** of sporadic encephalitis is **herpes simplex virus type 1.** HSV1
- Japanese encephalitis virus in Asia.
- Enterovirus type 71.
- West Nile virus.
- Saint Louis (St Louis) encephalitis virus.
- Eastern equine encephalitis virus.
- California encephalitis virus.
- Western equine encephalitis virus.
- **Uncommon causes:** varicella-zoster virus, Epstein-Barr virus, HIV, and human herpes virus-6.

Viral Pathogens in Postinfectious Encephalitis

- Mumps.
- Measles.
- Varicella-zoster virus.
- Rubella.
- Influenza.

Seasonal Incidence of Viral Encephalitis

Pak Time of Year	Viral Encephalitis
Summer	❖ West Nile virus ❖ Saint Louis encephalitis virus ❖ Eastern equine encephalitis virus ❖ California encephalitis virus ❖ Western equine encephalitis virus
Winter	❖ Mumps. ❖ Measles.
Any season	❖ Herpes simplex virus type 1 ❖ HIV

أي وقت بالسنة يجيو !

Clinical Features of Viral Encephalitis

1. **Prodromal symptoms:** fever, generalized malaise, headache, and myalgia. Some patients have respiratory signs (cough, sore throat). The headache is typically severe and may be associated with photophobia, nausea, and vomiting.
2. **Neurologic signs:**
   - Altered mental status.
   - Behavior and personality changes, and speech or movement disorders.
   - Motor or sensory deficits.
   - Movement disorder.
   - Discoordination.
   - Seizures. Tonic - clonic

Investigation

- ✓ **CBC, blood chemistry.**
- ✓ **Coagulation studies.**
- ✓ **CSF examination.** / LP
- ✓ **CSF and Blood cultures.**
- ✓ **CSF PCR:** CSF Polymerase Chain Reaction.
- ✓ **Neuroimaging:** brain CT, MRI. → هيبيبيد أوضح (لكل الحالات)
- ✓ **Brain biopsy:** brain biopsy can be considered in the patient if the etiology of encephalitis is still unknown.

لـ زعيم مرض جنون البقر

CSF Finding in Encephalitis

- Increased WBC count (a predominance of lymphocytes).
- Elevated protein concentration.
- Usually normal glucose concentration, but moderately reduced values are occasionally seen with **HSV and mumps.**
- Red blood cells are usually absent. Their presence in the appropriate clinical setting suggests **HSV-1 infection** or other necrotizing hemorrhagic encephalitis. } فى ↑ بتكون RBC

Neuroimaging

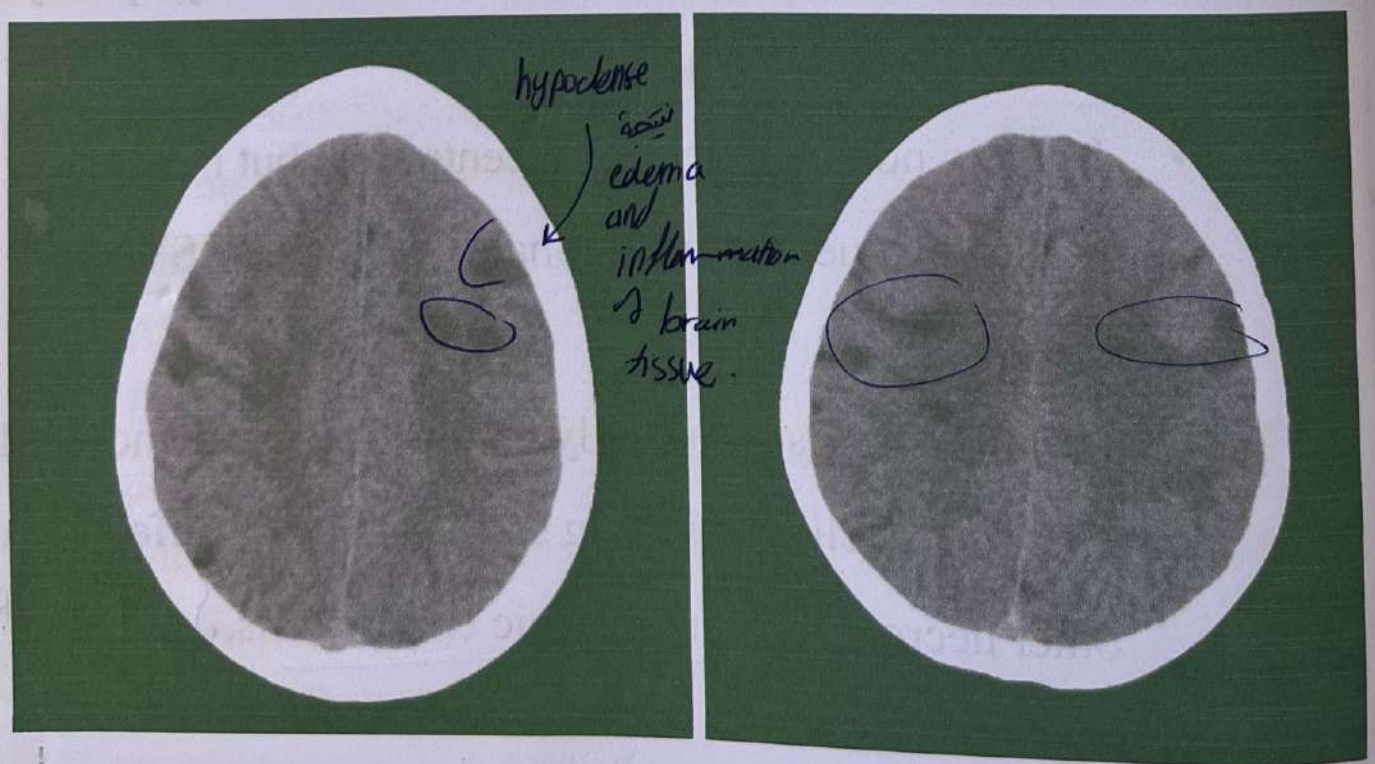
- Results of imaging in patients with encephalitis may or may not demonstrate abnormal radiographic findings on CT or MRI modalities.
- CT scanning is useful to rule space-occupying lesions or brain abscess.
- MRI is more sensitive for detecting inflammation and demyelination of the CNS.

CT/MRI ممكن يدلونا شو المسبب لل encen .

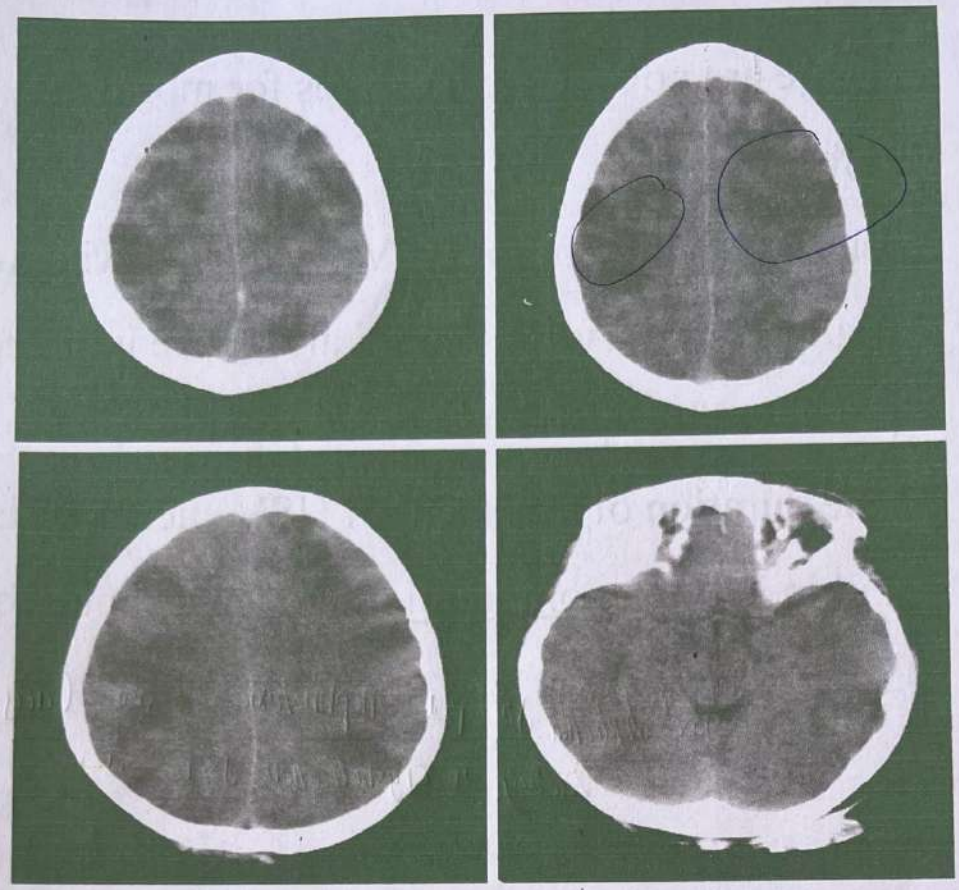
- **If present, the location of abnormal signal can sometimes be suggestive of specific etiologies:**
  - Temporal lobe involvement is strongly suggestive of HSV encephalitis.
  - The most common areas of involvement in eastern equine encephalitis are the basal ganglia and thalami.
  - In West Nile infection, MRI imaging demonstrated a variety of abnormalities in the basal ganglia, thalmi, temporal structures, brainstem and cerebellum.
  - The presence of hydrocephalus may suggest nonviral etiologies, such as bacteria, fungal, or parasitic agents

لانهم بزودوا ال fibrin وال adhesion ، ممكن تعمل obstruction بال CSF drainage

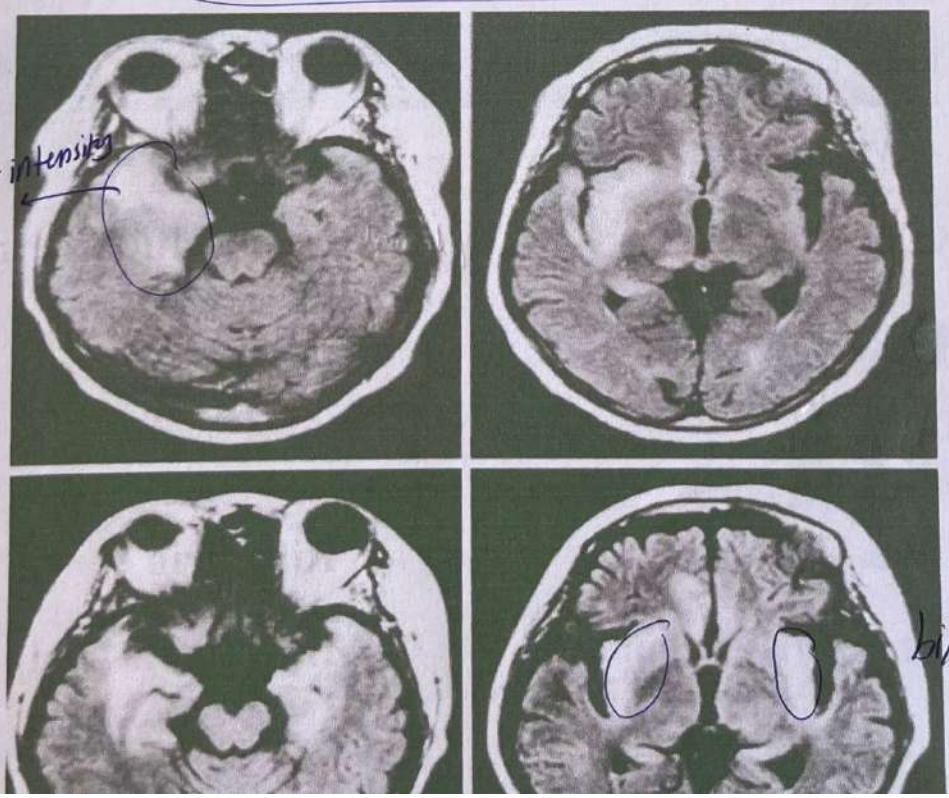
Acute Viral Encephalitis



Acute Viral Encephalitis



Brain MRI: Herpes simplex virus type 1 encephalitis



Therapy of Viral Encephalitis

- There are no specific therapies for most CNS viral infections.
- Empiric treatment for HSV-1 infection with **acyclovir (10 mg/kg IV every 8h)** should always be initiated as soon as possible if the patient has encephalitis.
- The duration of treatment of HSV encephalitis **10 days** and in immunocompromised patients should be **14 to 21 days.**

* (acyclovir) يعتبر nephrotoxic فلازم نعمل good hydration
عشان ما يعمل crystalization بال kidney

Suggested initial therapy for agents that cause encephalitis

Viruses	Drug Therapy
Cytomegalovirus →	Ganciclovir
Epstain-Barr	ملوش علاج No specific treatment
Herpes B virus →	Valgancyclovir
Herpes simplex →	Acyclovir
Human herpes virus 6 →	Ganciclovir
Measles →	Ribavirin
St. Louis encephalitis →	Interferon- 2 alpha
Varicella-zoster →	Acyclovir
West Nile	ملوش علاج No specific treatment